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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,892	03/26/2001	George Gow Brownlee	P02074US0	5755
26271	7590	03/24/2004	EXAMINER	
FULBRIGHT & JAWORSKI, LLP 1301 MCKINNEY SUITE 5100 HOUSTON, TX 77010-3095			WINKLER, ULRIKE	
			ART UNIT	PAPER NUMBER
			1648	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/674,892

Applicant(s)

BROWNLIE ET AL.

Examiner

Ulrike Winkler

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 and 48-56 is/are pending in the application.
- 4a) Of the above claim(s) 26 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-25, 28-40, 48-56 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☐ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date June 12, 2001.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Applicant's election with traverse of Group I in the response submitted December 22, 2003 is acknowledged. The traversal is on the ground(s) that applicants have amended the claims to "unify the inventive concept" and therefore the prior restriction should be withdrawn. This is not found persuasive because Bergmann et al. discloses the production of an attenuated influenza A virus in which the duplex region has been mutated (Journal of General Virology, 1995, see Figure 1, NA/X) . Therefore, the technical feature linking the inventions of groups I-III does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's second preliminary amendment submitted December 22, 2003 canceled claims 41-47 and added claims 48-56. Therefore, claims 1-25, 28-40 and 48-56 are currently under consideration.

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, received June 12, 2001, is attached to the instant Office Action.

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Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-25, 28-40 and 48- 56 are rejected under 35 U.S.C. 101 because the attenuated virus reads on a virus that can occur in nature wherein the virus is less virulent than another strain. The term mutated has not been defined in the specification in such a way as to clarify that naturally occurring viral variants are excluded from the term. It is well established in the art that viruses in nature mutate over time. Clarifying that the mutations are achieved using recombinant techniques would obviate the rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 7, 25, 30, 31, 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims make references to mutations at particular positions in relation to the 5' or 3' end of the nucleic acid structure, however the claims do not provide any indication which nucleic acid structure (specific isolate) these numbers are referencing. The claims make reference to a parent virus but do not identify the parent by a nucleic acid structure or a deposit. Furthermore, not all influenza viral structures will have adenine (A) at

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position 11' from the 5' terminus. Therefore, the instant claims are vague in that it is not clear what starting influenza virus structure the claims are referencing.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25, 28-40 and 48-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling the specific mutation of D1, D2, D3 and D1/2, does not reasonably provide enablement for predicting the effect of mutations having "functional modifications" or "functional equivalent substitutions at the same position" these modifications are either found in the non-coding region or they are in the coding region. The state of the art is unpredictable in this regard. Single mutations in the proximal promoter of influenza will not predictably result in an attenuated phenotype as determined by the activity of the promoter (see Flick et al. Promoter elements in the influenza virus vRNA terminal structure, RNA (1996) Vol. 2, pages 1046-1057, see figure 4) here some substitutions resulted in greater CAT activity. It is also not clear if the attenuation is due to a mutation in the coding region via the "functional modifications", substitutions in the coding regions have been found to result in the modification of the influenza virus activity (Castrucci et al. Attenuation of influenza A virus by insertion of a foreign epitope into neuramidase, Journal of Virology (1992) Vol. 66, No. 8, pages 4647-4653,

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see abstract). Additionally, there is a concern that a single mutation can result in a reversion to the original viral sequence, such a change would not be desirable for use of the virus as a live vaccine. Therefore, the invention is not enabled for the full scope of all possible combination contemplated and is enabled only for the specific mutation of D1, D2, D3 and D1/2 set out in the specification.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

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Claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Palese et al. (U.S. Pat. No. 6,022,726).

The instant invention is drawn to an attenuated influenza virus comprising a base pair substitution in the duplex region, which causes the protein coding region of the virus to be expressed at reduced levels in a cell, resulting in the attenuated phenotype.

Palese et al. disclose an attenuated genetically engineered influenza virus which contains at least one modification in the non-coding region comprising alteration to the stem structure of a promoter that down regulates synthesis of the modified viral gene segment so that some defective particles are produced (see claims 1). The attenuated virus produces subclinical infection in a patient (see claims 6). The specific example NA/B-NS shows a 5-10 fold reduced particle production (see column 14, lines 30-45). The reference also discloses the use of chimeric epitopes which results in an attenuated virus having 500-1000 fold lower LD50 levels (see column 17, lines 30-50). Therefore, the instant invention is anticipated by Palese et al.

Claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Palese P. (WO 93/21306).

The instant invention is drawn to an attenuated influenza virus comprising a base pair substitution in the duplex region, which causes the protein coding region of the virus to be expressed at reduced levels in a cell, resulting in the attenuated phenotype.

Palese et al. disclose an attenuated genetically engineered influenza virus which contains at least one modification in the non-coding region comprising alteration to the stem structure of a promoter that down regulates synthesis of the modified viral gene segment so that some

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defective particles are produced (see claims 1-3, 6, 15-17, 20, 24, 25, 26, 27, 28). The attenuated virus produces subclinical infection in a patient (see claims 15-17, 20). The specific example NA/B-NS shows a 5-10 fold reduced particle production . The reference also discloses the use of chimeric epitopes which results in an attenuated virus having 500-1000 fold lower LD50 levels (see pages 35-36). Therefore, the instant invention is anticipated by Palese P.

Claims 1-5, 8, 9, 12-18, 20-24, 28, 29, 33 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Bergmann et al. (Journal of General Virology, 1995, see IDS).

The instant invention is drawn to an attenuated influenza virus comprising a base pair substitution in the duplex region, which causes the protein coding region of the virus to be expressed at reduced levels in a cell, resulting in the attenuated phenotype.

Bergmann et al. disclose the construction of two influenza A virus that have mutations in the non-coding sequences (see figure 1) NA/X and NA/Y. NA/X and NA/Y both have reduced genomic RNA in infected cells (see figure 3), the RNA reduction was 5-7 fold for NA/Y and 3 fold for NA/X. These mutants were assayed for plaque formation in tissue culture using MDBK cells. The NA/Y mutant showed a 10 fold reduction compared to wild type and was found to be attenuated by at least 3 logs in the mouse inoculation assay. The reference indicates that a reduction in the expression of one viral component in the cell did not result in the packing of defective particles. The reduction in expression of one viral segment in a cell correlates with an attenuated viral phenotype in tissue culture and in the animal. Therefore, the instant invention is anticipated by Bergman et al.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-25 and 28-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. (Journal of General Virology, 1995), Bergmann et al. (Virus Research, 1996) and Kim et al. (Journal of General Virology, 1997) in view of Castrucci et al. (Journal of Virology, 1992)

The instant invention is drawn to an attenuated influenza virus comprising a base pair substitution in the duplex region, which causes the protein coding region of the virus to be expressed at reduced levels in a cell, resulting in the attenuated phenotype.

Bergman et al. teach the construction of two influenza A virus that have mutations in the non-coding sequences (see figure 1) NA/X and NA/Y. NA/X and NA/Y both have reduced

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genomic RNA in infected cells (see figure 3), the RNA reduction was 5-7 fold for NA/Y and 3 fold for NA/X. These mutants were then assayed for plaque formation in tissue culture using MDBK cells. The NA/Y mutant showed a 10 fold reduction compared to wild type and was found to be attenuated by at least 3 logs in the mouse inoculation assay. The reference indicates that a reduction in the expression of one viral component in the cell did not result in the packing of defective particles. The reduction in expression of one viral segment in a cell correlates with an attenuated viral phenotype in tissue culture and in the animal. The reference does not teach the specific mutations of the instant invention or inserting a heterologous gene into the attenuated nucleic acid construct.

Bergmann et al. teaches two influenza A/WSN/33 mutant viruses that have changes in the non-coding region of the 5' and 3' ends (see figure 1). The reference analyzed the effect of these mutation on the vRNA production in infected cells (see page 29, section 3.6). The NA/1+2 was almost 100 fold reduced as compared to the wild type virus and the partial revertants were slightly reduced. The reference teaches that the reductions in the viral titers correlates with the vRNA patterns in the cell. The reference does not teach mutations a position 11 and 10 from the 3' terminus or at position 11 and 12 from the 5' terminus.

Kim et al. teach mutations in the influenza A virus non-coding region and assays the ability to express CAT activity comparative to wild type. The reference teaches mutation in the 10-11' region of the 3' end and the 11-12' region of the 5' end (see figure 2). The mutations are assayed for their ability to express the protein product. The reference does not teach the correaltion of the reduced protein expression with an attenuated phenotype.

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Castrucci et al. teach that insertion of a heterologous sequence into the neuramidase gene of influenza virus results in the attenuation of the viral construct.

It would have been obvious to one of ordinary skill in the art at the time the invention was made utilize the mutations that Kim et al. has shown to be effective at reducing the expression of the protein coding sequence with the mutation in the promotor to produce an attenuated virus as taught by either Bergmann reference. One having ordinary skill in the art would have had a high expectation of success in applying these mutations because the art as shown in Bergmann et al. that reduced promoter activity correlates with a reduction in protein production which results in an attenuated phenotype of the virus. Adding an additional heterologous sequence into the attenuate influenza construct would be an obvious step to create a virus that exhibits an even greater attenuated phenotype. The art already has taught that insertion of a heterologous sequence into the influenza neuramidase gene will result in an attenuated phenotype.

The instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. One of ordinary skill in the art would have reasonably expected to obtain an attenuated influenza virus by having mutations in the promoter region in conjunction to adding a heterologous sequence.

Therefore, the instant invention is obvious over both Bergmann et al. references and Kim et al. in view of Castrucci et al.

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Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-56 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-10 of U.S. Patent No. 6,022,726. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are drawn to an attenuated influenza virus containing at least one modified non-coding region comprising alteration to the stem loop structure which down-regulates the synthesis of one viral gene segment.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294, please note after February 2004 the telephone number will change to 571-272-0912. The

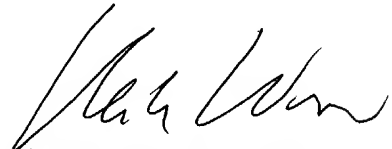
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examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The official fax phone number for the organization where this application or proceeding is assigned is 703-872-9306; for informal communications please use 703-746-3162, please note after February 2004 the fax phone number will change to 571-273-0912.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


ULRIKE WINKLER, PHD.
PATENT EXAMINER 3/22/04